Approval makes olaratumab the first first-line treatment option for soft tissue sarcoma in more than 40 years

When the US Food and Drug Administration approved olaratumab as a first-line treatment for patients with soft tissue sarcoma (STS) in the fall of 2016, it marked the first approval since the chemotherapy drug doxorubicin became standard of care more than 40 years ago.[1] Though rare, STS, which comprises a host of different histologic subtypes, has proven difficult to treat. Like pazopanib, which was approved in 2012 for the treatment of STS in the second-line setting, olaratumab targets the platelet-derived growth factor receptor alpha (PDGFRα), a tyrosine kinase receptor involved in cell signaling pathways that promotes key hallmark abilities in both cancer cells and the cells of the tumor microenvironment. Olaratumab, however, is a much more specific inhibitor of PDGFRα compared with pazopanib.

Accelerated approval was granted for the treatment of patients with STS that is not amenable to curative treatment with radiotherapy or surgery and with a subtype that cannot be treated effectively with an anthracycline-containing regimen. The approval was based on the phase 2 JGDG study, a randomized, active-controlled clinical trial in which 133 patients were randomized 1:1 to receive olaratumab plus doxorubicin, or doxorubicin alone.[2]

Eligible patients included those aged 18 years and over, with histologically confirmed diagnosis of locally advanced or metastatic STS not previously treated with an anthracycline, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (range, 1-5; 0, fully active and 5, dead), and with available tumor tissue for determination of PDGFRα expression by immunohistochemistry. Patients were enrolled at 16 clinical sites in 16 cities and 15 states in the United States from October 2010 to January 2013.

Patients were excluded if they had histologically or cytologically confirmed Kaposi sarcoma; untreated central nervous system metastases; received prior treatment with doxorubicin or other anthracyclines and anthracenediones, or any drug targeting PDGF or the PDGFRs; received concurrent treatment with other anticancer therapy within 4 weeks before study entry; unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction within 6 months before study entry; HIV infection; or if they were pregnant or lactating.

What's new, what's important

The approval of olaratumab as a first-line therapy for soft tissue sarcoma was based on data from a phase 2 trial in which 133 patients received olaratumab+doxorubicin or doxorubicin alone. Median PFS was increased by 6.6 months in the study group and 4.1 months in controls; improved ORR and OS were significant with olaratumab. The most common olaratumab-associated AEs include nausea, fatigue, and neutropenia, with more grade 3/4 AEs in the olaratumab patients than controls. The recommended is dose 15 mg/kg as an IV infusion on days 1 and 8 of each 21-day cycle, with doxorubicin for the first 8 cycles. Patients should be premedicated to protect against infusion-related reactions, and women should be informed about the risk of embryofetal toxicity and need for contraception. The drug should be administered in a setting with resuscitation equipment.

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Olaratumab was administered at 15 mg/kg as an intravenous infusion on days 1 and 8 of each 21-day cycle, and doxorubicin at 75 mg/m^2 as an intravenous infusion on day 1 of each cycle, for a maximum of 8 cycles. Patients were permitted to receive dexarozoxane on cycles 5-8 and crossover was permitted. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) every 6 weeks, and survival assessed every 2 months, until study completion. PDGFR expression was assessed by immunohistochemistry at a central academic laboratory before randomization.

The primary endpoint of the study was progression-free survival (PFS) and the combination of olaratumab–doxorubicin significantly extended PFS in this patient population: median PFS was 6.6 months in the combination arm, compared with 4.1 months in the doxorubicin-alone arm (hazard ratio [HR], 0.672; P = .0615). The objective response rate (ORR) and median overall survival (OS), which were secondary endpoints in the trial, were also significantly improved with combination therapy compared with doxorubicin alone (ORR, 18.2% vs 11.9%, respectively; median OS, 26.5 months vs 14.7 months). The benefits of combination therapy were observed across prespecified subgroups, including histological tumor type, number

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Mechanism of action: olaratumab

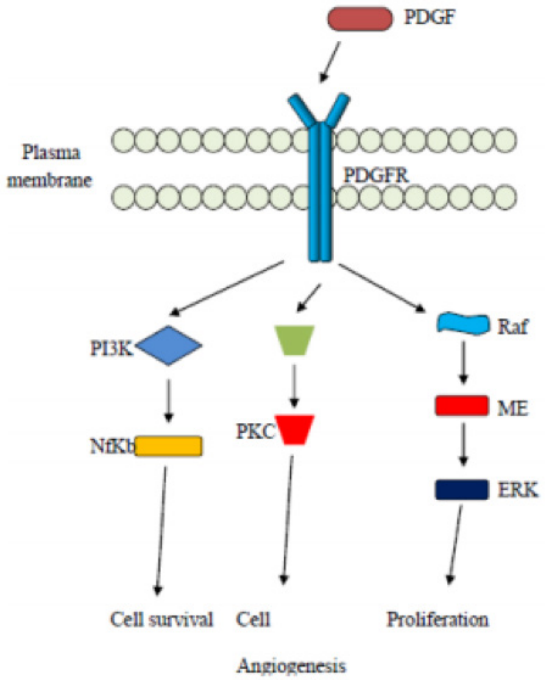
Blocking PDGFRα activity affects cancer cells and the microenvironment

There are 5 different platelet-derived growth factors (PDGFs) that bind to the extracellular parts of two different tyrosine kinase receptors, PDGFRα and β, expressed predominantly on the surface of mesenchymal cells, but to a lesser extent on a variety of other cell types.

Binding between ligand and receptor causes the receptor molecules to pair up, either with another receptor of the same type (homodimerization) or with the opposite type (heterodimerization). This leads to phosphorylation of the parts of the receptor found inside the cell and creates a docking site for signaling molecules within the cell that contain a particular domain. Among these molecules are SHP2, phosphatidylinositol 3-kinase, and signal transducer and activator of transcription, each of which orchestrate important signaling pathways in the cell that promote growth, survival, and migration, among other cellular processes.

The PDGFRs have been shown to be overexpressed in cancer cells and in the stromal cells of the surrounding microenvironment, as a means of promoting a variety of hallmark abilities, such as unrestricted growth, increased invasiveness, metastatic potential, and angiogenesis.

Olaratumab is a fully human immunoglobulin G1 monoclonal antibody that specifically inhibits the PDGFRα receptor, blocking the downstream signaling of this receptor in both tumor cells and stromal cells and inhibiting tumor cell growth and aberrant angiogenesis in the microenvironment.



Olaratumab specifically inhibits PDGFRα, a tyrosine kinase receptor that, upon binding of its ligands, initiates signaling pathways that play a role in the biology of mesenchymal and some other cell types. PDGFRα is overexpressed in numerous tumor types, including soft tissue sarcomas, and blocking its activity can have both direct effects on tumor cells and indirect tumor-suppressive effects in the microenvironment.

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of previous treatments, and PDGFRα expression level.

The most common adverse events (AEs) in the patients taking olaratumab were nausea, fatigue, neutropenia, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache. Grade 3/4 AEs were also higher for the combination than for doxorubicin alone. The most common AE leading to discontinuation of olaratumab was infusion-related reactions, which occurred in 13% of patients.

According to the prescribing information, the recommended dose for olaratumab is 15 mg/kg as an intravenous infusion over 60 minutes on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity, in combination with doxorubicin for the first 8 cycles. Patients should be premedicated with dexamethasone and diphenhydramine, to help protect against infusion-related reactions.

Olaratumab, marketed as Lartruvo by Lilly Oncology, has warnings and precautions relating to infusion-related reactions and embryofetal toxicity. Patients should be monitored for signs and symptoms of the former during and after infusion and olaratumab should be administered in a setting with available resuscitation equipment. Olaratumab should be permanently discontinued in the event of grade 3/4 infusion-related reactions. Olaratumab can cause fetal harm and female patients should be advised of the potential risk to a fetus and the need for effective contraception during treatment and for 3 months after the last dose.

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